REMARKS

Claims 1-31 and 42-45 are currently pending. Claims 1, 29, and 43 have been amended and new claim 46 has been added. No new matter has been added by way of this amendment. A marked up version of the new and amended claims is set forth in Appendix B. A clean version of the entire set of pending claims is submitted herewith as Appendix A for the Examiner's convenience.

Thus, after entry of this amendment, claims 1-31 and 42-46 will be pending in this application. Applicants respectfully request reconsideration of pending claims 1-31 and 42-46.

I. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 43 stands rejected under 35 U.S.C § 112, second paragraph, as allegedly being indefinite (Office Action, paragraph 2).

Solely in an effort to advance prosecution of this application, Applicants have amended claim 43 to recite a pharmaceutical composition comprising at least a first synthetic oligonucleotide according to claim 2 and a second synthetic oligonucleotide according to claim 2 in a pharmacologically acceptable carrier, wherein the first synthetic oligonucleotide and the second oligonucleotide are complementary to different non-contiguous regions of HCV. No new matter has been added by way of this amendment, and support can be found in the specification at page 15, lines 20-25.

Applicants submit that claim 43, as amended, satisfies the requirements of 35 C.F.R. § 112, second paragraph. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

II. Rejection Under 35 U.S.C. § 102(e).

Claims 1 and 44 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Cha *et al.* (U.S. Patent No. 6,071,693) ("Cha") (Office Action, paragraph 4).

While the Examiner acknowledges that SEQ ID NO:126 disclosed in Cha is only partially identical to SEQ ID NO:117, the Examiner opines that "there is a discrepancy between [SEQ ID NO:117] and the tables referred to by [claim 1]...Although the table teaches a mutation of SEQ ID NO:117, it does not teach SEQ ID NO:117, as it is claimed, and therefore the claim is contradictory" (Office Action, page 6).

Solely in an effort to advance prosecution of this application, Applicants have amended claim 1 to delete reference to SEQ ID NO:117. New claim 46 has been added and recites a synthetic oligonucleotide complementary to a portion of the 5' untranslated region of hepatitis C virus and having the nucleotide sequence SEQ ID NO: 117 (HCV-242, HCV-243, HCV-244), as set forth in Table 1A. The language in new claim 46 essentially corresponds to that of claim 1 and the pre-amended version of claim 29. Claim 29, *which was not rejected over Cha*, has also been amended to cancel its reference to SEQ ID NO:117, which is now found in new claim 46. Thus, no new matter has been added by way of this amendment.

Thus, Applicants submit that claim 1, as amended, and new claim 46 are not anticipated by Cha and satisfy all the requirements of 35 U.S.C. § 102(e). Likewise, claim 44, which is

dependent on amended claim 1 and new claim 46, and thus contains all the limitations thereof, also satisfies all the requirements of 35 U.S.C. § 102(e). Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

III. Rejection Under 35 U.S.C. § 103(a)

Several rejections under 35 U.S.C. § 103 have been made (Office Action, paragraphs 6-8). In order to respond completely and accurately, Applicants will address each ground separately below.

A. Hogan *et al.* and Maertens *et al.*

Claims 2-6, 8-20, 25, 27, 28, 30, and 43 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hogan *et al.* (U.S. Patent No. 5,424,413) ("Hogan") in view of Maertens *et al.* (U.S. Patent No. 5,846,704) ("Maertens") (Office Action, paragraph 6).

This ground of rejection is respectfully traversed.

Hogan discloses a nucleic acid probe having at least one nucleic acid strand, which has two separate target-specific regions that hybridize to a target nucleic acid. The Examiner cites Figure 4A in Hogan, to support the contention that these probes render the instant claims obvious (Office Action, page 4). However, as shown in Figure 5A, it is clear that these probes target contiguous regions on the target nucleic acid. Figure 5A is stated to be an "example of the general structure shown in Figure 4" (Hogan, Column 13, line 51). Thus, Figure 4A cited by the Examiner, does not render the instant claims obvious.

The Examiner also refers to column 3 of Hogan, which mentions that the "one or more nucleic acid molecules or the target nucleic acid may include nucleic acid adjacent the junction which does not form a duplex with the arm regions or the target regions or the target nucleic acid, and loops out from the junction." However, as was acknowledged by the Examiner, nowhere does Hogan suggest the use of synthetic oligonucleotides comprising a sequence complementary to at least two non-contiguous regions of an *HCV messenger or genomic RNA*.

To supply the deficiency in Hogan, the Examiner cites Maertens. The Examiner argues that a skilled artisan would have been motivated to target the probe of Hogan to an HCV messenger or genomic RNA because Maertens disclosed the importance of detecting HCV nucleic acids. However, the probes in Maertens target contiguous sequences from the 5' untranslated regions of HCV. In contrast, the oligonucleotides encompassed by the instant claims comprise a sequence complementary to at least two non-contiguous regions of HCV messenger or genomic RNA (see independent claim 2, from which the other rejected claims depend). Thus, the probes disclosed in Maertens do nothing to supply the deficiency of Hogan.

"To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *see also In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."'); *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (modification of the

teachings of a prior art reference is not established by the teachings of a second prior art reference "unless the prior art suggests the desirability of the modification"(emphasis added)). Applicants submit that the motivation to combine the cited references is completely lacking.

Respectfully, Applicants submit that the Examiner's use of hindsight-based obviousness analysis is inappropriate to determine the motivation of a skilled artisan at the time the application was filed. Further, nowhere does Maertens or Hogan suggest the desirability of utilizing the oligonucleotides of the instant invention comprising a sequence complementary to at least two non-contiguous regions of HCV messenger or genomic RNA. Therefore, Applicants submit that Maertens, either alone or in combination with Hogan, does not teach or suggest the use of synthetic oligonucleotides comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic DNA.

Thus, Applicants submit that independent claim 2 is non-obvious in view of the teachings of Hogan and Maertens. Similarly, claims 3-6, 8-20, 25, 27, 28, 30 and 43, wherein they depend directly or indirectly upon independent claim 2, and thus contain all the limitations thereof, also satisfy the requirements of 35 U.S.C. § 103(a).

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

B. Hogan *et al.*, Maertens *et al.*, and Seki *et al.*

Claims 7, 31, 43 and 45 have been rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Hogan, in view of Maertens, and in further view of Seki *et al.* (CA 2104649) ("Seki") (Office Action, paragraph 7).

This ground of rejection is respectfully traversed.

Hogan and Maertens have been discussed in detail above.

With respect to claim 7, the fact that Seki discloses SEQ ID NO:6, which is only partially identical to SEQ ID NO:47, does not render claim 7 obvious over the combined cited references, and does not supply the deficiencies of Hogan and Maertens. Claim 7 is dependent on claim 2, and thus, incorporates all the limitations thereof. Thus, claim 7 requires (1) that the oligonucleotide comprises a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA (see claim 2), and (2) that one portion of the oligonucleotide has the sequence SEQ ID NO:47 (see claim 7). SEQ ID NO:47 is a single sequence, which is specific for only one region of an HCV messenger or genomic RNA. It does not comprise another sequence portion complementary to at least one other non-contiguous region of an HCV messenger or genomic RNA, as required by claim 7, wherein it depends on independent claim 2. Furthermore, Seki does not disclose or suggest an oligonucleotide according claim 2 (which comprises a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA), wherein one portion of the oligonucleotide has the sequence SEQ ID NO:47. Instead, Seki merely discloses a sequence that may comprise one portion of an oligonucleotide that is complementary to at least two non-contiguous regions of the HCV messenger or genomic RNA.

With respect to claim 31, the fact that Seki discloses SEQ ID NO:229, which is only partially identical to SEQ ID NO:160, does not render claim 31 obvious over the combined cited references, and does not supply the deficiencies of Hogan and Maertens. Claim 31 is dependent

on claim 30, which in turn is dependent on claim 8, which in turn is multiply dependent on independent claims 1 or 2. For the reasons set forth above, neither Hogan nor Maertens disclose or suggest a synthetic oligonucleotide comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA, as is required by independent claim 2. Based on its dependency, claim 31 is not directed solely to an oligonucleotide having the nucleotide sequence of SEQ ID NO:160. Instead, claim 31 is directed to an oligonucleotide having the nucleotide sequence of SEQ ID NO:160, which is modified by incorporating at least one additional triplex forming strand (see claim 30).

Similarly, claims 43 and 45, which are pharmaceutical composition claims, are also not obvious over Hogan, Maertens or Seki for the same reasons outlined above with respect to claims 7 and 31.

Thus, neither Hogan, Maertens or Seki, alone or in combination, discloses or suggests the claimed oligonucleotides of claims 7 and 31 or the claimed pharmaceutical compositions of claims 43 and 45.

Applicants submit that claims 7, 31, 43 and 45 are non-obvious in view of the combined teachings of Hogan, Maertens, and Seki, and satisfy all the requirements of 35 U.S.C. § 103(a). Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

C. Hogan *et al.*, Maertens *et al.*, and Cha *et al.*

Claims 21 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hogan, in view of Maertens, and further in view of Cha *et al.* (U.S. Patent No. 6,071,693) ("Cha") (Office Action, paragraph 8).

This ground of rejection is respectfully traversed.

Hogan and Maertens have been discussed in detail above.

With respect to claim 21, the fact that Cha discloses SEQ ID NO:126, which is only partially identical to SEQ ID NO:122, does not render claim 21 obvious over the combined cited references, and does not supply the deficiencies of Hogan and Maertens. Claim 21 is directed to an oligonucleotide having the nucleotide sequence SEQ ID NO:122, as set forth in Table 1A. Table 1A shows various non-obvious modifications to SEQ ID NO:122. Specifically, Table 1A shows the following RNA sequence: uucgcgaccCAacacuacuc, wherein lower case letters represent 2'-O-methyl ribonucleotides and upper case letters represent deoxyribonucleotides (see footnote in Table 1A, page 25). In contrast, Cha discloses a DNA sequence, which comprises SEQ ID NO:122, but which does not disclose or suggest the modified form SEQ ID NO:122 that is set forth in Table 1A, and which is encompassed by claim 21. Moreover, none of Hogan, Maertens or Cha, either alone or in combination, discloses or suggests such an oligonucleotide.

With respect to claim 29, as discussed in detail above, Applicants have amended claim 29 to delete reference to SEQ ID NO:117. SEQ ID NO:117 is now encompassed by new claim 46 added herein.

SEQ ID NO:126 disclosed in Cha does not render new claim 46 obvious either alone or in combination with Hogan and Maertens. SEQ ID NO:126 disclosed in Cha is only partially identical to SEQ ID NO:117. Further, Table 1A shows various modifications to SEQ ID NO:117. Specifically, Table 1A shows the following sequences: TT*CGCGACCCAACACTACTC (HCV-242), TTCG*CGACCCAACACTACTC (HCV-243),

and TT*CG*CGACCCAACACTACTC (HCV-242), wherein *C represents 5-methyl-2'deoxycytidine (see last column in Table 1A, page 24). In contrast, Cha discloses a DNA sequence, which comprises SEQ ID NO:117, but which does not disclose the modified form SEQ ID NO:117 that is set forth in Table 1A, and which is encompassed by new claim 46. Moreover, none of Hogan, Maertens or Cha, either alone or in combination, discloses or suggests such an oligonucleotide.

Thus, Applicants submit that claims 21, 29 and new claim 46, are non-obvious in view of the teachings of Hogan, in view of Maertens, and further in view of Cha, and satisfy all the requirements of 35 U.S.C. § 103(a).

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

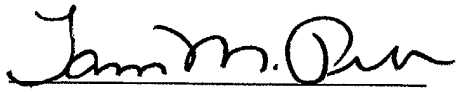
IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a one (1) month Extension of Time under 37 C.F. R. § 1.136(a) is filed concurrently herewith, which extends the response period from 28 January 2003 to 28 February 2003. The Petition further authorizes the PTO to charge the one month extension fee of $55 to our Deposit Account No. 08-0219, which reflects Applicants' Small Entity Status.

If there are any other fees due in connection with the filing of the response, please charge the fees to our Deposit Account No. 08-0219. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the Petition filed concurrently herewith, such an extension is requested and the fee should be charged to our Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,



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APPENDIX A

PENDING CLAIMS 1-31 and 42-46 (CLEAN VERSION)

1. (Amended) A synthetic oligonucleotide complementary to a portion of the 5' untranslated region of hepatitis C virus and having a nucleotide sequence selected from the group consisting of SEQ ID NOS:5, 6, 7, 8, 14, 15, 16, 23, 24, 26, 27, 28, 29, 31, 33, 36, 37, 47, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, and 133, as set forth in Table 1A, Table 1B, and Table 1F.

2. A synthetic oligonucleotide comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA.

3. An oligonucleotide according to claim 2, wherein the sequence is complementary to three non-contiguous regions.

4. A synthetic oligonucleotide according to claim 2, wherein one of the non-contiguous regions is the 5' untranslated region.

5. A synthetic oligonucleotide according to claim 3, wherein one of the non-contiguous regions is the 5' untranslated region.

6. An oligonucleotide according to claim 2 having about 18 to about 24 nucleotides.

7. An oligonucleotide according to claim 2, wherein one portion of the oligonucleotide has the sequence GGGGUCCUGGAG (SEQ ID NO:47) or has the sequence CAACACUACUCG (SEQ ID NO:80).

8. A synthetic oligonucleotide according to claims 1 or 2 which is modified.

9. An oligonucleotide according to claim 8, wherein the modification comprises at least on internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorothioate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, carboxymethyl ester, and combinations thereof.

10. An oligonucleotide according to claim 9 comprising at least one phosphorothioate internucleotide linkage.

11. An oligonucleotide according to claim 9, wherein the internucleotide linkages in the oligonucleotide are phosphorothioate internucleotide linkages.

12. An oligonucleotide according to claim 8 which comprises at least one deoxyribonucleotide.

13. An oligonucleotide according to claim 8 which comprises at least one ribonucleotide.

14. An oligonucleotide according to claim 12 which additionally comprises at least on ribonucleotide.

15. An oligonucleotide according to claim 14, wherein an oligodeoxyribonucleotide region is interposed between two oligoribonucleotide regions, or the inverted configuration thereof.

16. An oligonucleotide according to claim 13, wherein the ribonucleotide is a 2'-O-methyl ribonucleotide.

17. An oligonucleotide according to claim 14, wherein the ribonucleotide is a 2'-O-methyl ribonucleotide.

18. An oligonucleotide according to claim 15, wherein the ribonucleotide is a 2'-O-methyl ribonucleotide.

19. An oligonucleotide according to claim 14 which comprises at least one 2'-O-methyl ribonucleotide at the 3'-end of the oligonucleotide.

20. An oligonucleotide according to claim 19 which further comprises at least one 2'-O-methyl ribonucleotide at the 5'-end of the oligonucleotide.

21. An oligonucleotide according to claim 14 having a nucleotide sequence, selected from the group consisting of SEQ ID NOS:119-130, as set forth in Table 1A.

22. An oligonucleotide according to claim 2 comprising a sequence selected from the group consisting of SEQ ID NOS:38, 39, 40, 41, 42, 43, 44, 45, 46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, and 67, as set forth in Table 2.

23. An oligonucleotide according to claim 2 comprising a sequence selected from the group consisting of SEQ ID NOS:134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146 and 147, as set forth in Table 1C.

24. An oligonucleotide according to claim 3 comprising a sequence selected from the group consisting of SEQ ID NOS:148, 149, 150, 151, 152, 153, 154, 155, 156, 157, and 158, as set forth in Table 1D.

25. An oligonucleotide according to claim 8 which oligonucleotide is self stabilized by a loop.

26. An oligonucleotide according to claim 24 having a sequence selected from the group consisting of SEQ ID NOS:131, 132, and 133, as set forth in Table 1B.

27. An oligonucleotide according to claim 8, wherein the modification is selected from the group consisting of a nicked dumbell, a closed dumbell, 2', 3' and/or 5' caps, additions to the molecule at the internucleotide phosphate linkage, oxidation, oxidation/reduction, and oxidative/reductive amination, and combinations thereof.

28. An oligonucleotide according to claim 8, wherein at least one nucleoside is substituted by inosine or wherein at least one deoxycytosine is substituted by 5-methyl deoxycytosine.

29. (Amended) An oligonucleotide according to claim 28, having the nucleoide sequence SEQ ID NO:118 (HCV-245), as set forth in Table 1A.

30. An oligonucleotide according to claim 8, wherein the oligonucleotide is modified by incorporating at least one additional triplex-forming strand.

31. An oligonucleotide according to claim 30 having a nucleotide sequence selected from the group consisting of SEQ ID NOS:159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171 and 172, as set forth in Table 1E.

42. A pharmaceutical composition comprising at least two different oligonucleotides according to claim 1 in a pharmacologically acceptable carrier.

43. (Twice Amended) A pharmaceutical composition comprising at least a first synthetic oligonucleotide according to claim 2 and a second synthetic oligonucleotide according to claim 2 in a pharmacologically acceptable carrier, wherein the first synthetic oligonucleotide and the second oligonucleotide are complementary to different non-contiguous regions of HCV.

44. A pharmaceutical composition comprising at least one oligonucleotide according to claim 1 and a pharmacologically acceptable carrier.

45. A pharmaceutical composition comprising at least one oligonucleotide according to claim 2 and a pharmaceutically acceptable carrier.

46. (New) A synthetic oligonucleotide having the nucleotide sequence SEQ ID NO: 117 (HCV-242, HCV-243, HCV-244), as set forth in Table 1A.--

APPENDIX B

Amended Claims 1, 29 and 43, and New Claim 46 (MARKED UP VERSION)

Please amend claims 1, 29, and 43 as follows:

1. (Amended) A synthetic oligonucleotide complementary to a portion of the 5' untranslated region of hepatitis C virus and having a nucleotide sequence selected from the group consisting of SEQ ID NOS:5, 6, 7, 8, 14, 15, 16, 23, 24, 26, 27, 28, 29, 31, 33, 36, 37, 47, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, [117,] 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, and 133, as set forth in Table 1A, Table 1B, and Table 1F.

29. (Amended) An oligonucleotide according to claim 28, [wherein the oligonucleotide is selected from the group consisting of SEQ ID NOS:117 (HCV-242, HCV-243, HCV-244) and] having the nucleoide sequence SEQ ID NO:118 (HCV-245), as set forth in Table 1A.

43. (Twice Amended) A pharmaceutical composition comprising at least [two] a first synthetic [oligonucleotides] oligonucleotide according to claim 2 and a second synthetic oligonucleotide according to claim 2 in a pharmacologically acceptable carrier, wherein the [at least two] first synthetic [oligonucleotides] oligonucleotide and the second oligonucleotide are complementary to different non-contiguous regions of HCV.

Please add new claims 46 as follows:

--46. (New) A synthetic oligonucleotide having the nucleotide sequence SEQ ID NO: 117 (HCV-242, HCV-243, HCV-244), as set forth in Table 1A.--